# PTENT COOPERATION TREATOR

	From the INTERNATIONAL BUREAU			
PCT	То:			
NOTIFICATION OF ELECTION (PCT Rule 61.2)	Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202			
Date of mailing (day/month/year)	ETATS-UNIS D'AMERIQUE			
22 November 2000 (22.11.00)	in its capacity as elected Office			
International application No. PCT/GB00/01015	Applicant's or agent's file reference PWC/P30184WO			
International filing date (day/month/year)	Priority date (day/month/year)			
17 March 2000 (17.03.00)	23 March 1999 (23.03.99)			
Applicant				
CARR, Francis, J.				
1. The designated Office is hereby notified of its election made:    X   in the demand filed with the International Preliminary Examining Authority on:   13 October 2000 (13.10.00)   in a notice effecting later election filed with the International Bureau on:   2. The election   X   was   was not   was no				
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	Authorized officer			
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Zakaria EL KHODARY			
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38			

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			V., DEIRE	3E	Sweden		

# PATENT COOPERATION TREATY

PCT <sup>6</sup>

# **INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference		of Transmittal of International Search Report 220) as well as, where applicable, item 5 below.						
PWC/P30184W0	ACTION							
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)						
PCT/GB 00/01015	17/03/2000	23/03/1999						
Applicant								
BIOVATION LIMITED et al.								
This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.								
This International Search Report consists  X It is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	report.						
Basis of the report	<b></b>							
a. With regard to the language, the	international search was carried out on the bar ess otherwise indicated under this item.	sis of the international application in the						
the international search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of t	he international application furnished to this						
b. With regard to any nucleotide an was carried out on the basis of the		nternational application, the international search						
. —	nal application in written form.							
filed together with the inte	mational application in computer readable for	m.						
furnished subsequently to	this Authority in written form.	•						
furnished subsequently to	this Authority In computer readble form.							
the statement that the sub international application as	sequently furnished written sequence listing d s filed has been furnished.	loes not go beyond the disclosure in the						
the statement that the Info furnished	rmation recorded in computer readable form is	s identical to the written sequence listing has been						
2. Certain claims were four	nd unsearchable (See Box I).							
3. X Unity of invention is laci	dng (see Box II).							
4. With regard to the <b>title</b> ,								
X the text is approved as sul	omitted by the applicant.							
	ned by this Authority to read as follows:							
5. With regard to the abstract,								
X the text is approved as sul	omitted by the applicant.							
the text has been establish	ned, according to Rule 38.2(b), by this Authorit date of mailing of this international search rep	ty as it appears in Box III. The applicant may, oort, submit comments to this Authority.						
6. The figure of the drawings to be publi	·	<del></del>						
as suggested by the applic	ant.	None of the figures.						
because the applicant faile	d to suggest a figure.							
because this figure better	characterizes the invention.							
· · · · · · · · · · · · · · · · · · ·								

International Application No **≤**GB 00/01015

A. CLASSIFICATION OF SUBJECT MATTING TO THE CONTROL OF SUBJECT MATTING TO

C12N15/10

C07K16/00

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

 $\begin{array}{ll} \mbox{Minimum documentation searched} & \mbox{(classification system followed by classification symbols)} \\ \mbox{IPC 7} & \mbox{C12N} & \mbox{C07K} & \mbox{G01N} & \mbox{C12Q} \\ \end{array}$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J M KERR ET AL: "Encoded Combinatorial Peptide Libraries Containing Non-Natural Amino Acids" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 115, no. 115, 24 March 1993 (1993-03-24), pages 2529-2531-2531, XP002128603 ISSN: 0002-7863 page 2530, column 1; figure 1	1-35
	<b>-/</b>	

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents:  "A" document defining the general state of the art which is not considered to be of particular relevance  "E" earlier document but published on or after the international filing date  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  "O" document referring to an oral disclosure, use, exhibition or other means  "P" document published prior to the international filing date but later than the priority date claimed	T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  X* document of particular relevance; the claimed invention carnot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  *a* document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2000	08/08/2000
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswljk Tel. (+31-70) 340-2040, Tx. 31 651 epo rd, Fax: (+31-70) 340-3016	Hart-Davis, J

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International Application No GB 00/01015

C.(Continu	lation) DOCUMENTS CONSIDER OF O BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NIKOLAIEV V ET AL: "PEPTIDE RESEARCH. PEPTIDE-ENCODING FOR STRUCTURE DETERMINATION OF NONSEQUENCEABLE POLYMERS WITHIN LIBRARIES SYNTHESIZED AND TESTED ON SOLID-PHASE SUPPORTS" PEPTIDE RESEARCH,US,NATICK, MA, vol. 6, no. 3, 1993, pages 161-170, XP000867524 ISSN: 1040-5704 page 165; figure 1	1-35
Y	WO 95 16209 A (CIBA GEIGY AG ;FELDER EDUARD (CH); RINK HANS (CH); MATTHEWS IAN TI) 15 June 1995 (1995-06-15) page 26; claim 1; example 10 page 4, line 28, paragraph 4 - line 29	1-35
Y	WO 92 15679 A (PROTEIN ENG CORP) 17 September 1992 (1992-09-17) claims 1,2,26	1-35
X	CAO P ET AL: "Analysis of Peptides, Proteins, Protein Digests, and Whole Human Blood by Capillary Electrophoresis/Electrospray Ionization-Mass Spectrometry Using an In-capillary Electrode Sheathless Interface" JOURNAL OF THE AMERICAN SOCIETY FOR MASS SPECTROMETRY, US, ELSEVIER SCIENCE INC, vol. 9, no. 10, 1 October 1998 (1998-10-01), pages 1081-1088, XP004140548 ISSN: 1044-0305	36,38
Υ	page 1086, column 2, paragraph 2 -page 1087, column 2, paragraph 1	36,37, 40-43
X	VON LEOPRECHTING ACHIM; HOERTH PATRIC; HAEHNEL WOLFGANG; SCHILZ EMILE; MUEHLENHOFF ULRICH: "Identification of biotinylation sites on proteins by selective retrieval of 2-iminobiotinylated peptides from proteolytic peptide mixtures: Localization of the accessible lysine residues on the photosystem I subunits PsaD and PsaE" ANALYTICAL BIOCHEMISTRY, vol. 262, 10 September 1998 (1998-09-10), pages 110-121, XP002143247 the whole document	36,38, 44-51

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International Application No

0 (0		GB 00/01015
ategory °	ation) DOCUMENTS CONSIDE TO BE RELEVANT  Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
x	DUCDET AVEL , VAN COCTVEEN THEE, ENG TIMMY	26.20
\	DUCRET AXEL; VAN OOSTVEEN INGE; ENG JIMMY K; YATES JOHN R III; AEBERSOLD RUEDI:	36,38
	"High throughout protein characterization	
	by automated reverse-phase	
	chromatography/electrospray tandem mass	
	spectrometry"	
	PROTEIN SCIENCE, vol. 7, March 1998 (1998-03), pages	
	706-719, XP000922504	
	the whole document	36,37,
		40-43
	WANG BAIYANG; CHEN YI-BEN; AYALON ORAN;	36,37,
	BENDER JEFFRÉY; GAREN ALAN: "Human	40-43
	single-chain Fv immunoconjugates targeted	
	to a melanoma-associated chondroitin	
	sulfate proteoglycan mediate specific	
	lysis of human melanoma cells by natural killer cells and complement"	
	PROCEEDINGS OF THE NATIONAL ACADEMY OF	
	SCIENCES OF THE UNITED STATES OF AMERICA,	
	vol. 96, 16 February 1999 (1999-02-16),	
	pages 1627-1632, XP002143248	
	page 1628, column 2 	
, X	GENG M ET AL: "Signature-peptide approach	36,38
	to detecting proteins in complex mixtures"	
	JOURNAL OF CHROMATOGRAPHY, NL, ELSEVIER	
	SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 870, no. 1-2,	
	18 February 2000 (2000-02-18), pages	
	295-313, XP004187331	
	ISSN: 0021-9673	
	abstract 	
	P L COURCHESNE ET AL: "Identification of	36,37,
	Proteins by Matrix-Assisted Laser	40-43
	Description/Ionization Mass Spectroscopy	
	Using Peptide and Fragment Ion Masses (from 2-D Proteome Analysis Protocols, Ed.	1
	A. J. Link)"	
	METHODS IN MOLECULAR BIOLOGY,US,HUMANA	
	PRESS INC., CLIFTON, NJ,	
	vol. 112, no. 112, 1999, pages	
	487-511-511, XP002103063 page 491; figure 1	
	page 431, ligure 1	
		,
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information on patent family members

International Application No
PGGB 00/01015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9516209 A	15-06-1995	AU 1068295 A CA 2175078 A EP 0733213 A FI 962371 A	27-06-1995 15-06-1995 25-09-1996 07-06-1996
		HU 75223 A JP 9508355 T NO 962186 A	28-04-1997 26-08-1997 29-05-1996
WO 9215679 A	17-09-1992	US 5223409 A JP 7501203 T AU 1545692 A	29-06-1993 09-02-1995 06-10-1992
		AU 1578792 A AU 1581692 A AU 8740491 A	06-10-1992 06-10-1992 28-04-1992
		CA 2105300 A CA 2105303 A CA 2105304 A DE 573603 T	02-09-1992 02-09-1992 02-09-1992 06-05-1999
		EP 0575485 A EP 0573603 A EP 0573611 A	29-12-1993 15-12-1993 15-12-1993
		ES 2124203 T JP 7501923 T JP 6510522 T	01-02-1999 02-03-1995 24-11-1994
		US 5403484 A US 5571698 A WO 9206191 A	04-04-1995 05-11-1996 16-04-1992
		WO 9215677 A WO 9215605 A US 5663143 A US 5837500 A	17-09-1992 17-09-1992 02-09-1997 17-11-1998

# PATENT COOPERATION TREATY

# **PCT**

<sup>1</sup>REC'D 13 JUN 2001

# INTERNATIONAL PRELIMINARY EXAMINATION REPOR

(PCT Article 36 and Rule 70)

PWC/P30	r agent's file reference	FOR FURTHER ACTION		ation of Transmittal of Internat Examination Report (Form P				
International	application No.	International filing date (day/mont	h/year)	Priority date (day/month/yea	ar)			
PCT/GB00	0/01015	17/03/2000	•	23/03/1999	·			
	International Patent Classification (IPC) or national classification and IPC G01N33/532							
Applicant								
BIOVATIO	N LIMITED et al.							
	ternational preliminary exami transmitted to the applicant a	nation report has been prepare coording to Article 36.	d by this Inter	rnational Preliminary Exar	nining Authority			
2. This R	EPORT consists of a total of	13 sheets, including this cover	sheet.					
bed (se	en amended and are the bas	by ANNEXES, i.e. sheets of the is for this report and/or sheets of the Administrative Instructions sheets.	containing rec	tifications made before th	which have iis Authority			
3. This rep	port contains indications relat  Basis of the report	ing to the following items:						
i i	☐ Priority							
l "	-	pinion with regard to novelty, inv	entive step a	nd industrial applicability				
IV	□ Lack of unity of invention		omavo otop o	and modelina approaching				
V	☑ Reasoned statement un	der Article 35(2) with regard to ns suporting such statement	novelty, inver	ntive step or industrial app	licability;			
VI	☐ Certain documents cite	d						
VII	□ Certain defects in the infects	ternational application						
VIII	☑ Certain observations on	the international application						
			···					
Date of subm	ission of the demand	Date of	completion of the	nis report				
13/10/2000	)	·11.06.20	001	-				
	ailing address of the international camining authority:	Authoriz	ed officer		ASTRONO MICH			
<b>)</b>	European Patent Office D-80298 Munich Fel. +49 89 2399 - 0 Tx: 523656	Jacque	es, P					
,	Fax: +49 89 2399 - 4465	Telepho	ne No. +49 89 2	2399 8934	Dun D			

Applicant's or agent's file reference



<ol> <li>Bas</li> </ol>	is of	the	re	por	t
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1.	the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):  Description, pages:							
	1-4	0	as originally filed					
	Cla	ims, No.:						
	1-5	1	as originally filed					
ſ	Wit	h regard to the <b>lan</b> g guage in which the i	uage, all the elements marked above were available or furnished to this Authority in the nternational application was filed, unless otherwise indicated under this item.					
	The	ese elements were a	available or furnished to this Authority in the following language: , which is:					
		the language of a	translation furnished for the purposes of the international search (under Rule 23.1(b)).					
		the language of pu	blication of the international application (under Rule 48.3(b)).					
		the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).						
3.	With	n regard to any <b>nuc</b> rnational preliminan	leotide and/or amino acid sequence disclosed in the international application, the y examination was carried out on the basis of the sequence listing:					
		contained in the int	ernational application in written form.					
		filed together with the international application in computer readable form.						
	☐ furnished subsequently to this Authority in written form.							
		furnished subseque	ently to this Authority in computer readable form.					
	☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.							
		The statement that listing has been fur	the information recorded in computer readable form is identical to the written sequence nished.					
4.	The	amendments have	resulted in the cancellation of:					
		the description,	pages:					
		the claims,	Nos.:					
		the drawings,	sheets:					
5.		This report has bee considered to go be	en established as if (some of) the amendments had not been made, since they have been eyond the disclosure as filed (Rule 70.2(c)):					



(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6.	Ado	dditional observations, if necessary:							
IV.	Lac	k of unity of invention							
1.	In re	esponse to the invitation	to restri	ct or pay	additional fees the applicant has:				
		restricted the claims.							
		paid additional fees.							
		paid additional fees und	er prote	est.					
		neither restricted nor pa	id addit	ional fees	5.				
2.	×	This Authority found that 68.1, not to invite the ap	t the rec	quiremen to restrict	t of unity of invention is not complied and chose, according to Rule or pay additional fees.				
3.	This	Authority considers that	the req	uirement	of unity of invention in accordance with Rules 13.1, 13.2 and 13.3				
		complied with.							
	not complied with for the following reasons:								
4.	Con exar	sequently, the following prination in establishing t	parts of his repo	the interr rt:	national application were the subject of international preliminary				
	Ø	all parts.							
		the parts relating to clain	ns Nos.						
		easoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; ations and explanations supporting such statement							
1.	State	ement							
	Nov	, , ,	Yes: No:		1-35, 37, 39-51 36, 38				
	Inve	, , ,	Yes: No:	Claims Claims	1-35, 37, 39-51 36, 38				
	Indu		Yes: No:	Claims Claims	1-51				



2. Citations and explanations see separate sheet

### VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

# VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

# INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

# Re Item IV Lack of unity of invention

- 1. The separate groups of invention are:
  - group 1: claims 1-15
  - group 2: claims 16-20
  - group 3: claims 21-32
  - group 4: claims 33--35
  - group 5: claims 36-51

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

- the subject-matter of claim 1 is directed to a method of protein screening of a library of individual proteins wherein the contribution over the prior art appears to be the provision of a library of individual proteins wherein each of them includes in its sequence a "barcode" allowing the identification of the said protein.
- The subject-matter of claim 16 is also directed to a method of screening a protein library wherein the contribution over the prior art appears to be the dereplication of positively-binding pools to identify one or more individual proteins.
- The subject-matter of claim 21 is directed to another method of protein screening wherein the contribution over the prior art appears to be the provision of a library of individual proteins wherein each of them, together with its gene, is bound to an "associating moiety".
- The subject-matter of claim 33 is directed to a further method of protein screening wherein the contribution over the prior art appears to be the provision of a library of individual proteins wherein each of them is attached to an individual "coding moiety".

Although the said claims are all directed to methods for screening proteins libraries, it appears that the said methods do not share any common special technical feature.

-Moreover, the subject-matter of claim 36 is directed to a method of analysing a mixture of proteins. As the said subject-matter is already known (see point 8.1 under Item V), the subject-matter of the said claim does not provide any contribution over the prior art.

Thus, the requirements of unity of invention are not fulfilled in that there is no technical relationship among the inventions as they do not involve one or more of the same or corresponding special technical features. The expression "special technical features" means those features which define a contribution which each of the claimed inventions considered as a whole makes over the prior art.

### Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1. Reference is made to the following documents:
  - D1: WO 92 15679 A (PROTEIN ENG CORP) 17 September 1992 (1992-09-17)
  - D2: CAO P ET AL: 'Analysis of Peptides, Proteins, Protein Digests, and Whole Human Blood by Capillary Electrophoresis/Electrospray Ionization-Mass Spectrometry Using an In-capillary Electrode Sheathless Interface' JOURNAL OF THE AMERICAN SOCIETY FOR MASS SPECTROMETRY, US, ELSEVIER SCIENCE INC, vol. 9, no. 10, 1 October 1998 (1998-10-01), pages 1081-1088,
  - D3: DUCRET AXEL; VAN OOSTVEEN INGE; ENG JIMMY K; YATES JOHN R III: AEBERSOLD RUEDI: 'High throughout protein characterization by automated reverse-phase chromatography/electrospray tandem mass spectrometry' PROTEIN SCIENCE, vol. 7, March 1998 (1998-03), pages 706-719.
- The document cited as P-documents in the International Search Report is not to be 2. regarded as state of the art according to Article 33(2) PCT with regard to claims 36-51, as the date of priority claimed can be allowed for these parts of the present application.
  - With regard to claims 1-35, the date of priority claimed is not valid and thus the said document is part of the state of the art according to Article 33(2) PCT.
- 3. Document "VON LEOPRECHTING ACHIM et al., 'Identification of biotinylation sites on proteins by selective retrieval of 2-iminobiotinylated peptides from proteolytic peptide mixtures: Localization of the accessible lysine residues on the photosystem

I subunits PsaD and PsaE' ANALYTICAL BIOCHEMISTRY, vol. 262, 10 September 1998 (1998-09-10), pages 110-121" cited as an X-document in the ISR has not been considered as pertinent in the art as the said document relates to the determination of surface-exposed protein domains of proteins wherein a protein is chemically modified with 2-iminobiotin, digested by Glu-C and Arg-C protease, fractionated by avidin agarose batch and HPLC before being analysed by mass spectrometry. However, the said method is not concerned with the digestion of a protein mixture. and thus is not a method suitable for analysing mixtures of proteins.

#### 4. Group 1 (claims 1-15):

- 4.1 Notwithstanding the objection raised under Article 6 PCT (see point 2 under Item VIII), it would appear that the subject-matter of claim 15 refers to a library wherein each individual protein includes in its sequence a "barcode sequence", which can be used to identify each individual protein in the library.
  - As the particular combination of features of independent claim 15 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).
- 4.2 Moreover, the subject-matter of the said claim would appear to involve an inventive step in the sense of Article 33(3) PCT for the following reasons:
  - The closest state of the art is considered to result from document D1.
  - This document discloses improved libraries of display phage which display various protein domains with potential to bind to a target material of interest wherein sitespecific protease cleavable linkers may be incorporated (see abstract).

The subject-matter of claim 15 is distinguished therefrom in that each individual protein includes in its sequence a "barcode sequence" and no display system is present.

The technical effect of this distinguishing feature results in identifying which protein has bound to the specific target.

The technical problem to be solved by the invention was therefore the provision of improved libraries allowing the identification of individual protein without the need of any display system.

**EXAMINATION REPORT - SEPARATE SHEET** 

Tha said technical problem has convincingly been solved by including in each protein of the library a "barcode sequence". As the said solution is not disclosed nor suggested in the cited prior art, the subject-matter of claim15 involves an inventive step in the sense of Article 33(3) PCT.

4.3 Notwithstanding the objection raised under Article 6 PCT (see point 1 under Item VIII), as the subject-matter of claim 1 relates to a method of screening the new and inventive protein library of claim 15 (see above points 4.1 and 4.2), the same reasoning as for the said claim applies to claim 1 which is new (Article 33(2) PCT) and involves an inventive step (Article 33(3) PCT). The same applies to dependent claims 2-14.

#### 5. Group 2 (claims 16-20):

- Notwithstanding the objection raised under Article 6 PCT (see point 3 under Item VIII), as the particular combination of features of independent claim 16 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).
- 5.2 Moreover, the subject-matter of the said claim would appear to involve an inventive step in the sense of Article 33(3) PCT for the following reasons: it would appear that the technical problem to be solved is similar to the one mentioned above (see point 4.2), and has been convincingly solved by screening pools of proteins in solution, followed by the precipitation of the total pool prior to mass analysis, especially MALDI-TOF, in order to screen for a "fingerprint" of jonised peaks which is representative of the target and therefore indicates if the target has bound. A positively-binding pool is then dereplicated to reduce the complexity of the pool.

As the said solution is not disclosed nor suggested in the cited prior art, the subjectmatter of claim 16 involves an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 17-20.

#### 6. Group 3 (claims 21-32):

- 6.1 Notwithstanding the objection raised under Article 6 PCT (see point 4 under Item VIII), as the particular combination of features of independent claim 21 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).
- 6.2 Moreover, the subject-matter of the said claim involves an inventive step in the sense of Article 33(3) PCT for the following reasons:

The subject-matter of claim 21 is distinguished from the closest prior art D1 (see above point 4.2) in that a library of individual protein is screening wherein each individual protein together with its gene, is bound to an "associating moiety".

The technical effect of this distinguishing feature results in identifying which protein has bound to the target.

The technical problem to be solved by the invention is thus similar to the one mentioned above (see point 4.2).

It has convincingly been solved by binding both the protein and its gene to an "associating moiety".

As the said solution is not disclosed nor suggested in the cited prior art, the subjectmatter of claim 21 involves an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 22-32.

#### 7. Group 4 (claims 33-35):

- Notwithstanding the objection raised under Article 6 PCT (see point 6 under Item 7.1 VIII), as the particular combination of features of independent claim 33 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).
- 7.2 Moreover, the subject-matter of the said claim involves an inventive step in the sense of Article 33(3) PCT for the following reasons: the technical problem to be solved is similar to the one mentioned above (see point

4.2) and has been solved by the provision of a "coding moiety" wherein each individual protein of the library is attached to the said "coding mojety".

As the said solution is not disclosed nor suggestd in the cited prior art, the subjectmatter of claim 33 would appear to involve an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 34-35.

#### 8. Group 5 (claims 36-51):

8.1 The subject-matter of claim 36 is not new (Article 33(2) PCT) for the following reasons:

document D2 discloses the analysis of a mixture of horse heart cytochrome c and myoglobin. The said protein mixture was first digested with trypsin, the resultant peptides were fractionated by capillary electrophoresis before being analysed by mass spectrometry (see page 1086, left column, 21 to right column, line 12).

Document D3 discloses a method for protein identification wherein enzymatic digests of either homogeneous polypeptides or simple protein mixture were generated and fractionated by reverse-phase chromatography electrospray before being analysed by mass spectrometry.

Thus, all the features of claim 36 are already known from D2 or D3.

The same applies to dependent claim 38.

8.2 The features of dependent claim 37 are not disclosed in the cited prior art, and therefore its subject-matter is considered to be new (Article 33(2) PCT).

Moreover, the subject-matter of the said claim would appear to involve an inventiv step in the sense of Article 33(3) PCT for the following reasons:

the subject-matter of the said claim differs from D2 or D3 (see above point 8.1) in that the fractionation step (ii) is carried out using a library of protein binding agents.

The technical effect of this distinguishing feature results in the fractionation of larger mixture of peptides.

The technical problem to solved was therefore to provide a method for analysing

large mixtures of peptides.

The said problem has been convincingly solved by using a library of protein binding agents to fractionate the peptides resulting from the digestion step.

As the said solution is not disclosed nor suggested in the cited prior art, the subject-matter of claim 37 would appear to involve an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 40, 41, 42, 43.

8.3 The features of dependent claims 39 (see however the objection under Art. 6 PCT in point 7 of Item VIII), 44, 45, 48 and 51 are not disclosed in the cited prior art, and therefore they subject-matter is considered to be new (Article 33(2) PCT).

Moreover, it would appear that all these dependent claims relate to different embodiments having the same effect as mentioned above (see point 8.2) which is the sub-fractioning of the mixture of proteins or resultant peptides.

Thus, it would appear that the technical problem to be solved by the said claims is the same as mentioned above (see point 8.2) which is to provide a method for improving the analysis of large mixtures of proteins.

As none of the cited prior art discloses nor suggests any of these embodiments for sub-fractioning a peptide mixture or peptide fragments in combination with a method for analysing mixtures of proteins, it would appear that the subject-matter of claims 39, 44, 45, 48 and 51 involve an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 46, 47, 49 and 50.

### Re Item VII

## Certain defects in the international application

 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

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# Re Item VIII

### Certain observations on the international application

- The subject-matter of claim 1 is not clear (Article 6 PCT) for the following reasons: 1. - the subject-matter for which the protection is sought is not defined. A method claim should be defined in the procedural steps necessary to carry out the said method. - furthermore, the term "barcode sequence" is vague and unclear for the skilled man
  - and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.
- 2. The subject-matter of claim 15 is not clear (Article 6 PCT) for the following reasons: - the subject-matter of the said claim is directed to a library of proteins. The said library is defined by referring to claims directed to steps of a method for screening the said library.
  - Thus, as the said claim does not clearly define the library by mentioning all its essential technical features, the definition of the subject-matter of said claim is unclear.
- 3. The subject-matter of claim 16 is not clear (Article 6 PCT) for the following reasons: - the subject-matter for which the protection is sought is not defined. A method claim should be defined in the essential procedural steps necessary to carry out the said method, in the present case, for example, that pool of proteins are precipitated, and then analysed by mass spectrometry to screen for a fingerprint of ionised peaks which is representative of the target, positively-binding pools being dereplicated to reduce the complexity of the pool.
  - furthermore, the term "dereplication" is vague and unclear for the skilled man and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.
- The subject-matter of claim 21 is not clear (Article 6 PCT) for the following reasons: 4.
  - the subject-matter for which the protection is sought is not defined. A method claim should be defined in the procedural steps necessary to carry out the said method,
  - furthermore, the term "associating moiety" is vague and unclear for the skilled man and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.

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- 5. The subject-matter of claim 23 is unclear (Article 6 PCT) as the term "dereplicated" is vague and unclear for the skilled man and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.
- The subject-matter of claim 33 is not clear (Article 6 PCT) for the following reasons: 6. - the subject-matter for which the protection is sought is not defined. A method claim should be defined in the procedural steps necessary to carry out the said method. - furthermore, the term "coding moity" is vague and unclear for the skilled man and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.
- 7. The subject-matter of claim 39 is not clear (Article 6 PCT) for the following reasons: - the said claim is directed to the addition of one or more amino acids to the resultant peptides. However, as all the essential steps of this method are not defined (notably the step of terminal protease cleavage, as described on page 23 of the description), the subject-matter for which the protection is sought is not clearly identified. A method claim should be defined in the essential procedural steps necessary to carry out the said method